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(54) Title: COLLAGEN COMPOSITES FOR CONTROLLED DRUG RELEASE

(57) Abstract

A crosslinked, collagen-base, controlled-release delivery system is provided comprising a binding agent incorporated into the collagen and a pharmacologically active material, such as an antibiotic, absorbed into the crosslinked collagen incorporating the binding agent. The delivery system is particularly useful as a corneal shield for delivery of antibiotics or other drugs to the eye.

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COLLAGEN COMPOSITES FOR
CONTROLLED DRUG RELEASE

5 FIELD OF THE INVENTION

The present invention is directed to collagen composites from which a drug may be loaded and released in a controlled manner. The present invention is particularly directed to collagen 10 composites from which drugs having ophthalmic use may be released in a controlled manner.

BACKGROUND OF THE INVENTION

In many drug delivery systems, involving percutaneous, subcutaneous or other in vivo 15 application, a smooth release profile is desired to limit the adverse response to the drug or to prolong the duration of drug action. In particularly sensitive body tissues, such as the eye, careful control of the release of the drug is especially 20 important and the type of substrate carrying the drug is somewhat limited since it must be transparent, thin, non-toxic, nonantigenic and nonimmunogenic as well as capable of bearing a sufficient load of the drug to be practically useful to combat the disorder 25 or infection which is being treated.

Collagen, in the form of a thin film, gel, or microspheres, is a particularly attractive substrate for this purpose. However, the problem of adapting collagen materials for a sufficient load of drug and 5 a smooth release profile sufficient for use within the eye has not been heretofore, it is believed, adequately solved.

One approach for altering the characteristics of collagen to attempt to tailor its drug release 10 characteristics is disclosed in U.S. Patent 4,164,559 to Miyata et al. Collagen membranes are prepared wherein the collagen is modified by esterification and/or acylation, however, this chemical modification may unacceptably alter the collagen and create 15 irritation and/or immunogenic reactions. Miyata et al. also describe proteolytic enzyme processing of collagen, however, this may also affect antigenicity and/or immunogenicity of the collagen.

In U.S. Patent 4,291,013 to Wahlig et al. there are 20 disclosed collagen compositions from which active ingredient release may be attenuated by use of a resorbable binding agent. The preferred resorbable binding agents are polymers of glycolic acid and lactic acid, as well as their co-polymers in various 25 weight ratios of the monomer units. Other disclosed resorbable binding agents are polyamino acids. The binding agent is used by mixing the binding agent, active ingredient and collagen by homogenization or other means and then pressing, sintering or melting 30 the mixture. The shaping of the mixture is then carried out according to conventional synthetic resin processing technology under action of pressure and/or heat. The composition containing the active ingredient, binding agent and collagen is apparently 35 fully resorbed into the body. It is not believed

th the process described in ~~this~~ patent is applicable for making collagen composites wherein it is desired for the collagen to remain essentially intact while the drug is slowly released from the 5 collagen in a controlled manner. It is believed that the invention described in this patent is not particularly useful for making collagen composites for ophthalmic use since it appears that the method of release of the drug is primarily by resorption of 10 the entire composite, rather than by slow release of the drug from a substrate.

It is therefore an object of the present invention to provide collagen from which there is controlled release of a drug when in contact with body fluids or 15 tissues, particularly when in contact with the eye.

This and other objects of the invention will be apparent from the following description, from the appended claims as well as from practice of the invention.

20 SUMMARY OF THE INVENTION

The present invention provides a collagen-based drug delivery system for use in contact with body fluids and/or tissues comprising an ionic, and/or hydrophobic or hydrophilic binding agent incorporated 25 into collagen, where the binding agent is absorbed or formulated into the collagen and crosslinked into the collagen ~~or~~ covalently linked to the collagen, and further comprising a pharmacologically active material absorbed into the crosslinked collagen, 30 where the amount of and/or strength of the binding of the active material in the collagen is enhanced by attraction between the ionic, hydrophobic and/or hydrophilic binding agent and the active material to control the release of and/or attenuate the rate of

release of the material from the collagen into the body fluid and/or tissue.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph of sequential uptake and delivery
5 of collagen corneal shields unmodified or modified
with ionic binding agents sodium alginate or
polyquaternary ammonium cellulose, where the drug is
simulated by the anionic marker sodium fluorescein.

Fig. 2 is a graph of the release of the drug
10 gentamicin from collagen films modified with the
ionic binding agent sodium alginate.

Fig. 3 is a graph of the release of the drug
Gentamicin from collagen which has been modified with
the ionic binding agent sodium alginate or
15 quaternized cellulose.

Fig. 4 is a graph of the release rate of sodium
fluorescein from collagen containing the ionic
binding agent sodium alginate or quaternized
cellulose.

20 Fig. 5A is a graph of the uptake of dexamethasone as
a function of weight of PEG - cholesteryl sebacate
binding agent in a composite collagen film.

Fig. 5B is a graph of the bound fraction of
dexamethasone as a function of weight of PEG -
25 cholesteryl sebacate binding agent in a collagen
film.

Fig. 6 is a graph of the uptake of cortisone as a
function of weight of PEG - cholesteryl sebacate
binding agent in a composite collagen film.

Fig. 7 is a graph of dexamethasone elution from a PEG - cholesteryl sebacate - modified composite collagen film.

Fig. 8A is a graph of a log y-axis plot of the data
5 in Fig. 7, indicating the rate of elution of
dexamethasone.

Fig. 8B is a graph of the half-life of release of
dexamethasone from a PEG - cholesteryl sebacate-
modified collagen film as a function of the bound
10 fraction of dexamethasone in the film.

DETAILED DESCRIPTION OF THE INVENTION

Non-antigenic, non-immunogenic substrates for
delivery of drugs to body tissues and fluids are
highly desirable particularly in sensitive areas,
15 such as the eye. Collagen is an excellent material
for delivery of drugs in that tissue since it readily
hydrates for comfort and has a slow rate of
dissolution in tears.

The collagen used in accordance with the present
20 invention may comprise soluble or insoluble collagen
of the types I, II, III and IV and mixtures thereof.
Soluble collagens (types I, II, III and IV) may be
prepared by known methods such as by enzymatic
digestion of tissue enriched in such collagen types.
25 Insoluble collagens may be derived from typical
sources such as bovine and chicken tendons and bovine
and chicken bones (all type I); bovine articular
cartilage, nasal septum, sternal cartilage (all type
II) and bovine and human aorta and skin (types I and
30 III).

Methods of extraction and purification of various collagen material from such tissues are known and may vary somewhat, depending upon the nature of the collagen source. Tropocollagen or procollagen

- 5 comprises the sodium chloride extract from collagen sources such as cartilage and bone. Mild acid extracts from collagen sources (such as by mild acetic acid extraction after removal of the more soluble substances through self-extraction) produces
- 10 a greater yield of "acid soluble" collagen.

Extraction may also be performed by limited cleavage by enzymes which preferentially degrade non-collagenous proteins (pepsin, papain, etc.).

- 15 The binding agents utilized in accordance with the present invention are believed to improve not only the loading but also the release of the drug from the collagen by tailoring the charge characteristics of the collagen-binding agent composite to complement the ionic charge, hydrophobicity and/or

- 20 hydrophilicity of the bioactive agent. Unmodified collagen binds to both anionic and cationic bioactive agents due to the presence of both acidic and basic amino acid moieties in the collagen, however the binding agent improves the loading and release

- 25 characteristics. In general, when dealing with a negatively charged or anionic bioactive agent, a positively charged or cationic binding agent should be utilized. When dealing with a cationic bioactive agent, then an anionic binding agent should be
- 30 utilized.

Unmodified collagen binds to hydrophilic bioactive agents and to a lesser extent, to hydrophobic bioactive agents. However, an appropriate binding agent improves the loading and release

- 35 characteristics of the bioactive agent. Particularly

preferred are polymeric binding agents, such as, alginate and polyethyleneglycol derivatives which improve the loading and release characteristics in collagen of such drugs as tobramycin or dexamethasone

5 (a steroid), respectively, as compared to unmodified collagen. In general, increasing hydrophobicity of the bioactive agent will require increase of the hydrophobicity of the binding agent to achieve appropriate loading and release profiles.

10 Some of the binding agents include, but are not limited to: sodium alginate (a relatively hydrophilic polyanion available from kelp), carboxylated cellulose (a hydrophilic polyanion, derived from wood); polyacrylic acid and derivatives

15 thereof (a hydrophilic polyanion which may be synthesized); glycosoaminoglycans (a hydrophilic polyanion, isolatable from animal tissues); polygalacturonic acid (a polyanion isolatable from citrus peels); pectin (a polyanion isolatable from

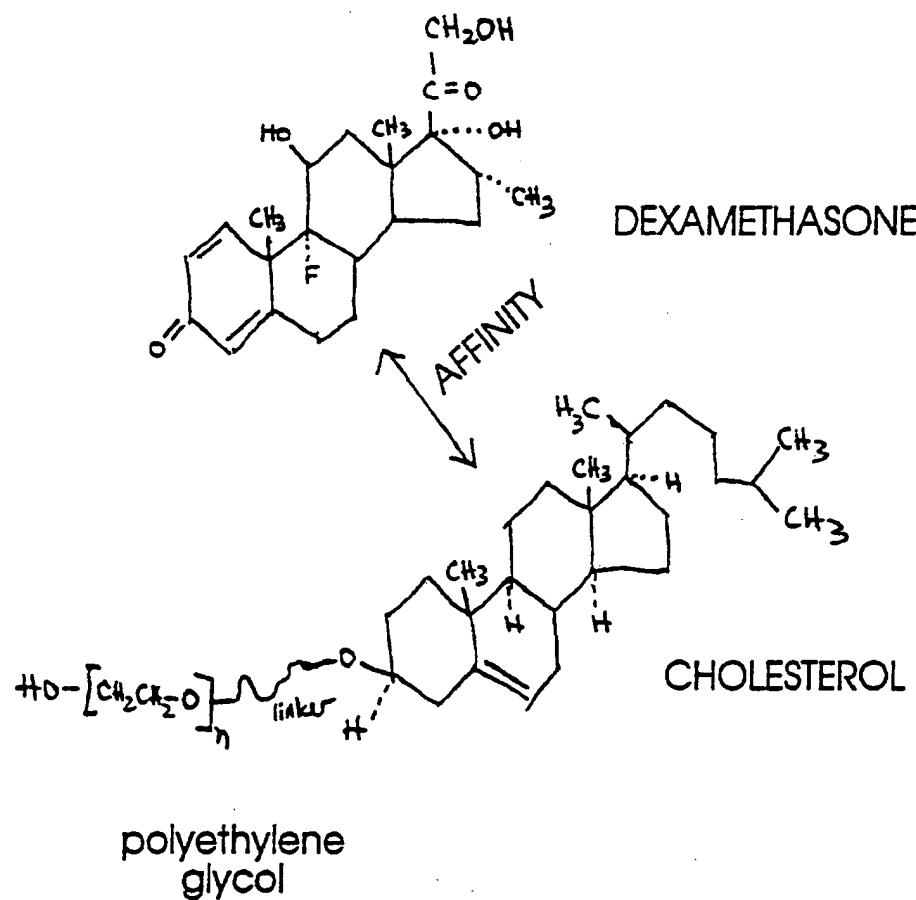
20 citrus peels); carboxylated collagen (polyanions isolatable from animal tissues); dextran sulfate (polyanion, which may be synthesized); quaternized cellulose (polycations from chemically derivitized wood); polyethyleneglycol (a synthetic polymer) and

25 derivatives thereof; spermine/spermidine (polycations isolatable from animals); chitin/chitosan (polycations isolatable from arthropods) and aminated collagen (polycation from chemically derivitized collagen isolatable from animal tissues).

30 Of particular advantage for hydrophobic bioactive agents is the use of a polyalkyleneglycol derivative of the bioactive agent as the binding additive. The coupling of polyethyleneglycol, for example, through a linking group, such as, sebacic acid, to a

35 hydrophobic analogue of the hydrophobic bioactive

agent renders the analogue water soluble. The resulting derivatives are miscible with collagen solutions and can be incorporated into collagen materials. The hydrophobic portion of the binding 5 additive can provide specific hydrophobic binding attraction to the hydrophobic bioactive agent. A specific example is the use of polyethyleneglycol derivative of cholesterol, a biochemical precursor to steroids, as a binding agent to provide affinity for 10 steroids such as dexamethasone:



Methods of linking polyalkyleneglycols to other compounds are known in the art. For example, polyalkylene glycol may be linked to the hydroxy group of a sterol through a bifunctional linking 15 agent which reacts with hydroxy groups, such as,

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diacids (succinic acid, glutaric acid, sebamic acid, etc.). Particularly preferred binding agents are polyethyleneglycol - and polypropyleneglycol-containing compounds.

- 5 A further improvement is attained in that the drug release rate is prolonged as compared to drug release from collagen, thus reducing the frequency of replacement of the drug delivery vehicle in the body. The polyalkyleneglycol-modified steroids include, but
- 10 are not limited to, PEG-cholesterol derivatives, PEG-testosterone derivatives, PEG-estradiol derivatives, PEG-cortisone derivatives and the like.

The collagen and the binding agent are typically mixed in any convenient manner. A preferred method

- 15 is to form an aqueous collagen dispersion, mix it with the binding agent, cast a dispersion into an appropriate mold, and then dry. The relative amounts of the collagen to binding agent will vary but in general about 2% by weight of the binding agent to
- 20 20% by weight may be utilized to retain the essential physical characteristics of the collagen and yet to impart sufficient appropriate ionic and/or hydrophobic or hydrophilic character to the collagen to obtain a desired load and release rate.
- 25 Other methods may be utilized to physically mix the collagen with the binding agent, such as by formulating dry mixtures of collagen and binding agent, then forming an aqueous suspension thereof.

The collagen-binding agent composites may then be

- 30 treated to crosslink the collagen by conventional methods such as by dehydration, ultraviolet irradiation, by use of chemical crosslinking agents such as a carbodiimide, N-hydroxysuccinimide derived

from active esters, etc. Examples include succinimide active esters such as N-hydroxysuccinimide, 3,3'-dithio (sulfosuccinimidyl propionate and bis- (sulfosuccinimidyl) suberate. In 5 some instances, the binding agent may be covalently linked directly to the collagen, particularly if the molecular weight and size of the binding agent is such that collagen crosslinking is not sufficient to prevent loss of the binding agent when the composite 10 is in an environment for releasing or for re-loading of the active agent from or into the composite.

Crosslinking reagents and conditions, for both collagen crosslinking and covalent linking of the binding agent to the collagen, are known to those of 15 ordinary skill in the art. For example, when using a succinimidyl active acid ester crosslinking agent the collagen-binding agent composite is immersed in a solution of the crosslinking agent typically at a concentration from about 0.1 to about 15.0% (w/v) and 20 maintained at a temperature from about 2° to 40°C for a period of time of about 1 to 96 hours.

Alternatively and preferably, crosslinking may be performed by dehydration of the intermediate collagen involves heating from about 50° to 200°C typically in 25 a vacuum of about 50 millitorr or less for about 1 to 96 hours (so-called "dehydro thermal crosslinking" method).

Alternatively, the crosslinking agent may be premixed with the collagen and/or binding agent prior to 30 drying.

It will be realized that the degree of crosslinking (i.e., controlled by the conditions and/or the amount of crosslinking reagent), may be readily determined by those of ordinary skill in the art to attain the

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uptake and/or release characteristics of the particular drug which are desired from the collagen composite. Furthermore, the amount of crosslinking may be adjusted to limit to an acceptable minimum the 5 amount of the binding agent which may be leached from the composite during use in the body fluids. It is intended that the crosslinking will prevent the binding agent from being released from the composite so that the primary substance being released from the 10 composite into the body fluid will be the bioactive agent, the release characteristics of which are tailored by the ionic, hydrophobic and/or hydrophilic interaction with the binding agent. Moreover, since the binding agent is essentially retained within the 15 composite, the composite may be reloaded in situ with the bioactive agent. For example, a composite which is a corneal shield may be reloaded by use of liquid drops containing the bioactive agent. The bioactive agent, or at least some of it, will be absorbed into 20 and adsorbed onto the shield, then slowly released over time. This reloading of the composite may continue in situ until the composite is dissolved by the bodily fluids.

A particular advantage of the present invention is 25 that the binding agent will increase the bound fraction of the bioactive agent in the collagen composite as compared to the bound fraction of the bioactive agent in collagen not modified with the binding agent. In a given sample of collagen 30 composite (or other absorbent material) immersed into and in equilibrium with a fluid containing the bioactive agent, the amount of bioactive agent in the composite in excess of the amount due to passive fluid absorption is considered the bound portion. 35 The percentage of the bioactive agent which is bound

($K_b \times 100$) can be calculated as shown in the examples.

The bioactive agents which may be utilized according to the present invention include but are not limited

- 5 to glaucoma treatment agents such as beta-blockers, epinephrine, carbonic anhydrase inhibitors, prostaglandin derivatives and pilocarpine, gentamicin (a cationic drug), tobramycin, amikacin, butirosin, didesoxykanamycin, fortimycin, kanamycin,
- 10 lividomycin, neomycin, netilmycin, etc.; chloramphenicol and its derivatives such as thiamphenicol, erythromycins, lactone antibiotics such as novobiocin, leucomycins such as spiramycin, lincomycins such as clindamycin; anesthetics;
- 15 macrolides such as rosamycin; quinolones; penicillins such as ampicillin; peptide antibiotics such as bacitracin, rifamycins; heparin; steroids such as dexamethasone, etc.; streptomycins, tetracyclones such as tetracycline, cephalosporins, as well as
- 20 other antibiotics such as cycloserine, etc.

Preferred antibiotics are tobramycin, gentamicin and quinolones. It is also contemplated that combinations of two or more of the bioactive agents may be utilized, such as combinations including anti-

- 25 inflammatory agents, wound healing promoters other desirable agents which may be distributed at the target site in the body and which may be bound to the collagen composite. In order to bind combinations of bioactive agents, it may be necessary to incorporate
- 30 combinations of binding agents into the collagen.

The bioactive agent is preferably absorbed by soaking the collagen-binding agent composite in a solution containing the bioactive agent, drying and rehydrating before time of use in the eye (or other

- 35 body tissue) or rehydrating at the time of use in a

solution containing the bioactive agent. It will be realized that the amount of bioactive agent which will be loaded onto the composite will depend upon the amount of binding agent which is present (i.e.,

5 ionic hydrophobic and/or hydrophilic attraction of the binding agent to the bioactive agent), upon the concentration of the bioactive agent in the solution into which the composite is soaked, as well as the length of time in which the composite remains in such

10 solution. It is within the skill of those of ordinary skill in the art to determine the proper amount of loading depending upon the release profile and instantaneous dosage which is desired for the drug at the site of the body tissue.

15 The composite may be in any convenient form for use in or near a body tissue or cavity, such as a film, microspheres, monolithic shapes, sponges, etc. Corneal shield films and microsphere suspensions are particularly useful.

20

EXAMPLE 1

To illustrate the invention, collagen corneal shields were made containing, in the first case, sodium alginate as an anionic binding agent and, in a second case quaternized cellulose. An unmodified collagen

25 corneal shield was used as a control. The samples were sequentially loaded and eluted with sodium fluorescein (a model for an anionic drug).

Referring to Fig. 1, results are shown of the above-described test with the abscissa showing the number

30 of times the shields were loaded and eluted, and the ordinate showing the ratio of the drug eluted to the total amount of drug which absorbed in the loading stage, normalized to the control (unmodified

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collagen). After loading the shields, the sodium fluorescein was effluxed or allowed to release into physiological solution and the shield was then reloaded with a drug containing solution. Referring 5 to Fig. 1, the drug loading and release shows a substantial enhancement of drug binding with the cationic quaternary compound (the drug is an anionic compound) and the drug repulsion effect with the anionic sodium alginate. Sequential drug loading and 10 release shows that the polymeric ionic additive is effective in maintaining the drug affinity over several loading and release cycles although a slight loss of 13% is seen at the third cycle. This demonstrates, for example, that the ionic binding 15 agent has essentially been permanently incorporated into the collagen and allows the corneal shield to be recharged with the drug in situ, for example by the use of the drug in eye drop form.

Referring to Table 1, collagen films containing 20 various amounts of binding agents (sodium alginate, quaternized cellulose, chitosan, or carboxymethylcellulose) were hydrated in drug containing solutions and their fluid swell values calculated to assess drug concentration as a function 25 of fluid volume absorption. The films were then eluted into a tear buffer and the total drug concentration measured.

To calculate the fraction of drug bound to the material, the total drug incorporated is corrected 30 for the passively absorbed drug due to fluid uptake.

$$\text{Total Drug} = \text{Bound Fraction} + \text{Free Fraction}$$

$$1 = \frac{\text{Bound Fraction}}{\text{Total Drug}} + \frac{\text{Free Fraction}}{\text{Total Drug}}$$

$$1 = K_b + K_f$$

Since $K_f = \text{Fluid absorbed by material} \times \text{Drug concentration of surrounding fluid}$, K_b can be readily calculated from the equilibrium binding results.

TABLE 1

	<u>Collagen Additive</u>	<u>Description</u>	<u>$K_b \times 100$ Gentamicin, @ 4 wt%</u>	<u>$K_b \times 100$ Penicillin @ 10 wt%</u>	<u>$K_b \times 100$ Fluorescein, @ 5 Mm</u>	<u>$K_b \times 100$ Fluorescein, @ 1 Mm</u>
5	None	Collagen Alone	22.5%	21.3%	61.7%	79.5%
	10% Alginate	Polyanion	73.2%	29.5%	42.0%	
	20% Alginate	Polyanion	71.5%		24.9%	
	10% Quat Cellulose	Polycation	14.8%	48.8%	71.6%	
10	20% Quat Cellulose	Polycation		6.6%	79.9%	
	20% Chitosan	Polycation				89.9%
	20% CarboxyMethyl Cellulose	Polyanion	34.9%			

15 It is evident from the results that cationic drug gentamicin has a low binding affinity for collagen alone, but the binding attraction is increased with the addition of polyanions and decreased with the addition of polycations. Penicillin, an anionic drug, also demonstrates low binding affinity for collagen, and remains almost unchanged with the addition of polyanions, but increased significantly with the addition of polycation additive. Fluorescein, an anionic diagnostic dye, shows strong natural binding attraction to collagen alone. However even in this case, the binding affinity is increased with the addition of cationic polymeric additives and reduced with the addition of anionic additives.

Referring to Fig. 2, there is shown a graph of three sets of films: a collagen loaded with 2.0% by weight sodium alginate, 10% by weight sodium alginate, and a control collagen. All of these were loaded with 5 gentamicin and the release profile tested for four hours. As shown in Fig. 2, in similarly treated films, the sodium alginate-loaded collagen delivered more drug during the first two hours after exposure to the tear buffer than did the control. Subsequent 10 to two hours, the release rate in all films tended to level off rather uniformly.

Referring to Figs. 3 and 4, are shown the release rates of sodium fluorescein (Fig. 3) and gentamicin (Fig. 4) from collagen films containing a binding 15 agent sodium alginate or quaternized cellulose.

Referring to Fig. 3, it can be seen that in the composite containing anionic drug (sodium fluorescein) and cationic binding agent (quaternized cellulose) more drug was released than from the film 20 containing the anionic binding agent sodium alginate.

Referring to Fig. 4, it can be seen that the release of the cationic drug gentamicin is enhanced in the collagen bearing the anionic binding agent (sodium alginate), whereas release is depressed in the 25 collagen bearing the cationic binding agent, quaternized cellulose.

EXAMPLE 2

Collagen slurries were prepared in deionized water at between 1.25% and 2.0% solids and Ph of 8.0+/-0.2. 30 An appropriated volume of 2% polyethyleneglycol-cholesteryl sebacate (PEG-C) solution was stirred into this mixture to yield a predetermined ratio of collagen to PEG-C in the final dried film. Solution was cast into hemispherical polypropylene molds with 35 a base curve of 8.6 mm and dried under controlled

conditions. The dried films were crosslinked under heated vacuum (dehydrothermal crosslinking) for an appropriate amount of time to yield the desired hydration of the finished product. This product

5 referred is to hereafter as a (corneal) shield. After drying and dehydrothermal crosslinking, the collagen composite swells up to 1000% but does not release PEG-C when soaked in aqueous buffers at room temperature.

10 Dry shields (ten) were weighed and placed into saturated steroid solutions in tear buffer. Drug uptake by the shield did not change after the first few minutes of soaking, indicating that uptake was no slower than the hydration of the shield. Thus

15 shields were soaked for a convenient length of time, typically one to two hours. The wet shields were weighed and transferred into clean dry vials. A known amount of trypsin/buffer solution was added and the tubes were incubated at 37°C for two to four

20 hours or until the shields appeared completely dissolved by visual inspection. This solution was assayed for dexamethasone using HPLC and UV detection. From the dry and wet weights of the shield and the soaking solution concentration, the

25 amount of drug passively soaked up by the shield could be determined. The remainder of the assayed drug was assumed to be bound in some manner to the composite matrix. The uptake of shields ranging from 0 to 20% POE-C was determined.

30 Since the volume of the tear film is 7-10 μ l, and the volume of the hydrated shield is typically 25 μ l, an exact model of the delivery of drug to the tear film from a corneal shield was not possible. A small volume cell was machined which would allow good

35 mixing between inlet solution and solution in the

cell. A sample cell was loaded with a pre-soaked corneal shield. Buffer was pumped into the sample cell through two inlets at right angles to each other to afford good mixing of the cell contents. Eluted 5 solution was continuously pumped through the injection loop of an HPLC autosampler system (Spectra-Physics SP8780). At predetermined times, an injection onto a C18 column was made from the 10 contents of the injection loop. By injecting the eluate directly onto a column, the complication of small volume sample collection were overcome. Standard peak analysis was performed, and a plot of 15 elution concentration versus time was generated for both 100% collagen and 20% PEG-C composite collagen shields.

Figure 5A shows a plot of total dexamethasone uptake for shields of various composition soaked in aqueous saturated dexamethasone solutions. The x-axis shows the amount of PEG-C incorporated into the collagen 20 shield, ranging from 0 to 20% incorporation. The solid squares represent the calculated amount of dexamethasone passively soaked up by the shields due to swelling. The open squares show the total amount 25 of drug taken up by the shields. The difference between total uptake and uptake due to swell normalized to total drug content is the bound drug fraction, K_b . It is most apparent from this graph that the addition of increasing amounts of PEG-C to the collagen shield greatly increases the amount of 30 dexamethasone bound by the shield. This is more clearly illustrated in Fig. 5B which shows the increase in K_b for dexamethasone as related to the amount of PEG-C in the composite collagen material. Figure 6 is a plot summary of a similar uptake 35 experiment run with the steroidal compound cortisone in the soaking solutions. Again, the same behavior

of increased drug binding at higher weight fractions of PEG-C in the shield is shown. Figures 7 and 8 show elution profiles for the 100% collagen and 20% PEG-C shields. Figure 7 is a linear y-axis plot
5 which shows that dexamethasone is released at much higher concentrations throughout the release experiment. The area under the PEG-C release curve is roughly four times the area under the 100% collagen release curve, which is in agreement with the drug
10 uptake results. Figure 8A is a log y-axis plot of the same data shown in Figure 7. From this plot it is apparent that not only is the dexamethasone releasing at a higher concentration from the modified shield, but that it is also releasing at a slower
15 rate. The extended half-life of drug release due to the binding additive is illustrated in Fig. 8B, showing the increase in drug half-life as related to PEG-C additive levels.

20 The data presented above demonstrate a novel method of enhancing and sustaining uptake and release of steroidal drugs from collagen hydrogels.

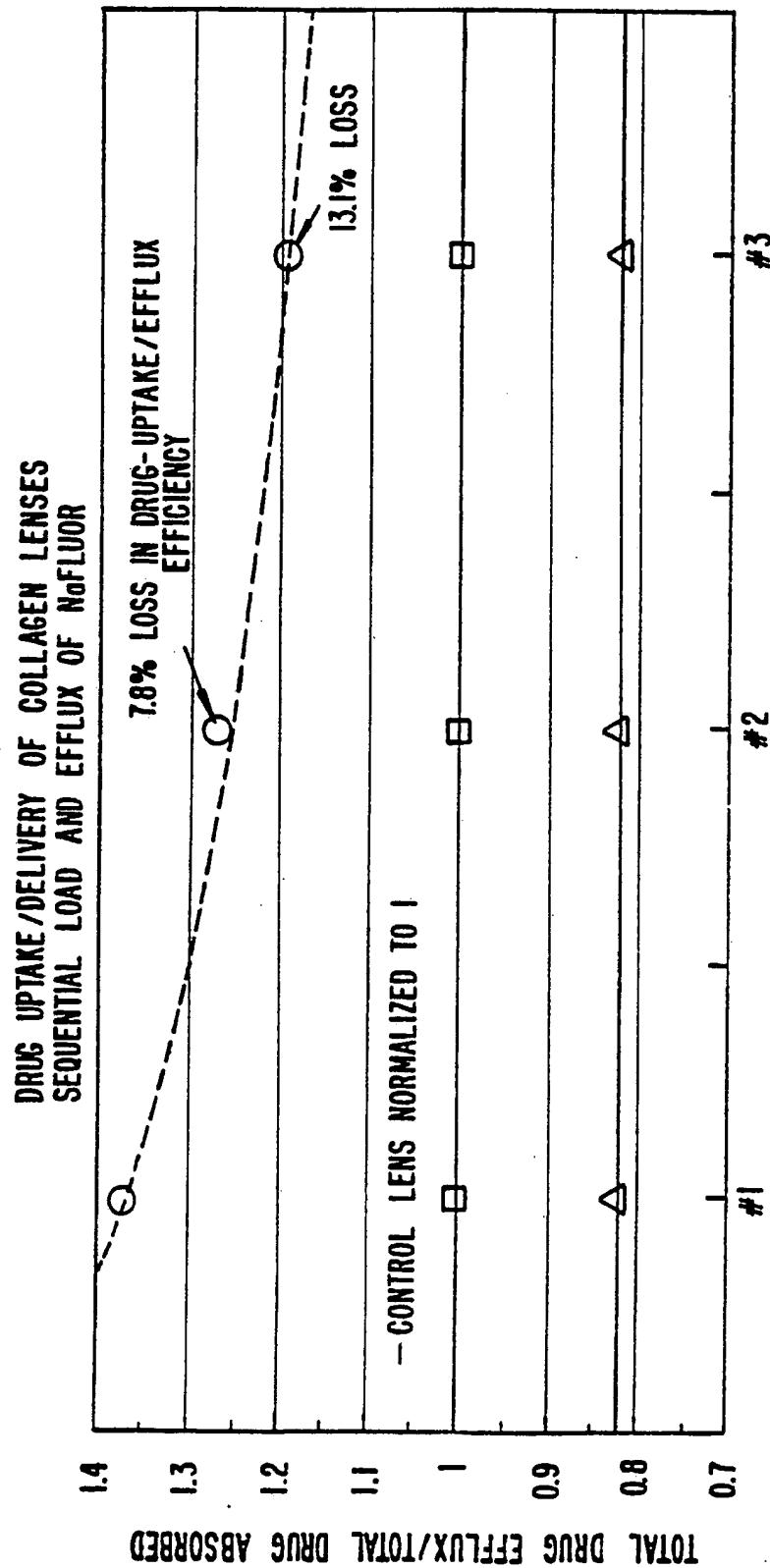
WHAT IS CLAIMED IS:

1. A crosslinked collagen-based control-release delivery system for use in contact with body fluid or tissue comprising:
 - 5 (a) a binding agent incorporated into said collagen; and
 - 10 (b) a pharmacologically active material absorbed into said collagen incorporating said binding agent, whereby the amount and/or strength of binding of said active material in said collagen is altered by ionic, hydrophobic, and/or hydrophilic interaction between said binding agent and said active material to enhance or attenuate the rate of and/or amount of release of said material from said collagen into said body fluid or tissue.
 - 15
 2. A system according to Claim 1 characterized by a bound fraction, K_b , of said pharmacologically active material greater than the bound fraction of said pharmacologically active material measured in similar collagen not incorporating said binding agent.
 3. A system according to Claim 1 wherein said binding agent is incorporated into said collagen by contacting said binding agent with said collagen and crosslinking said collagen.
 - 25 4. A system according to Claim 1 wherein said binding agent is incorporated into said collagen by covalently linking said binding agent to said collagen.
 - 30 5. A system according to Claim 1 wherein said binding agent is selected from the group consisting of alginate, quaternized cellulose, chitosan, polyacrylic acid-containing compounds,

pol yleneglycol-containing compounds and carboxymethylcellulose.

6. A system according to Claim 5 wherein polyalkyleneglycol-containing compounds are selected 5 from the group consisting of polyethyleneglycol- and polypropyleneglycol-containing compounds.
7. A system according to Claim 1 wherein said pharmacologically active material comprises an antibiotic.
- 10 8. A system according to Claim 1 wherein said active material comprises a growth factor.
9. A system according to Claim 1 wherein said active material comprises a steroid.
10. A system according to Claim 1 wherein said 15 active material comprises an agent for glaucoma treatment.
11. A system according to Claim 1 wherein said collagen is crosslinked by thermal dehydration.
12. A system according to Claim 1 wherein said 20 collagen is crosslinked by chemical crosslinking agents.
13. A system according to Claim 1 in the form of a corneal shield.
14. A system according to Claim 1 in the form of 25 microspheres.
15. A system according to Claim 1 in the form of an ocular insert.

16. A system according to Claim 7 wherein said active material comprises tobramycin.
17. A system according to Claim 7 wherein said active material further comprises dexamethasone.
- 5 18. A system according to Claim 1 wherein said binding agent comprises a polyalkyleneglycol-modified drug analogue.
19. A system according to Claim 18 wherein said drug analogue comprises a steroid.
- 10 20. A system according to Claim 18 wherein said modified drug analogue comprises polyethyleneglycol-cholesteryl sebacate.
21. A system according to Claim 20 wherein said pharmacologically active material comprises a steroid.
- 15 22. A system according to Claim 20 wherein said pharmacologically active material comprises dexamethasone.
23. A system according to Claim 20 wherein said pharmacologically active material comprises cortisone.
- 20 24. A system according to Claim 1 comprising two or more different binding agents.
25. A system according to Claim 1 comprising two or more different pharmacologically active materials.



- PERFORM 3 LOAD-EFFLUX CYCLES PER LENS
- COMPARE EFFECT OF ANIONIC/CATIONIC ADDITIVES
- MEASURE ABILITY OF LENS TO "RELOAD"

FIG. 1.

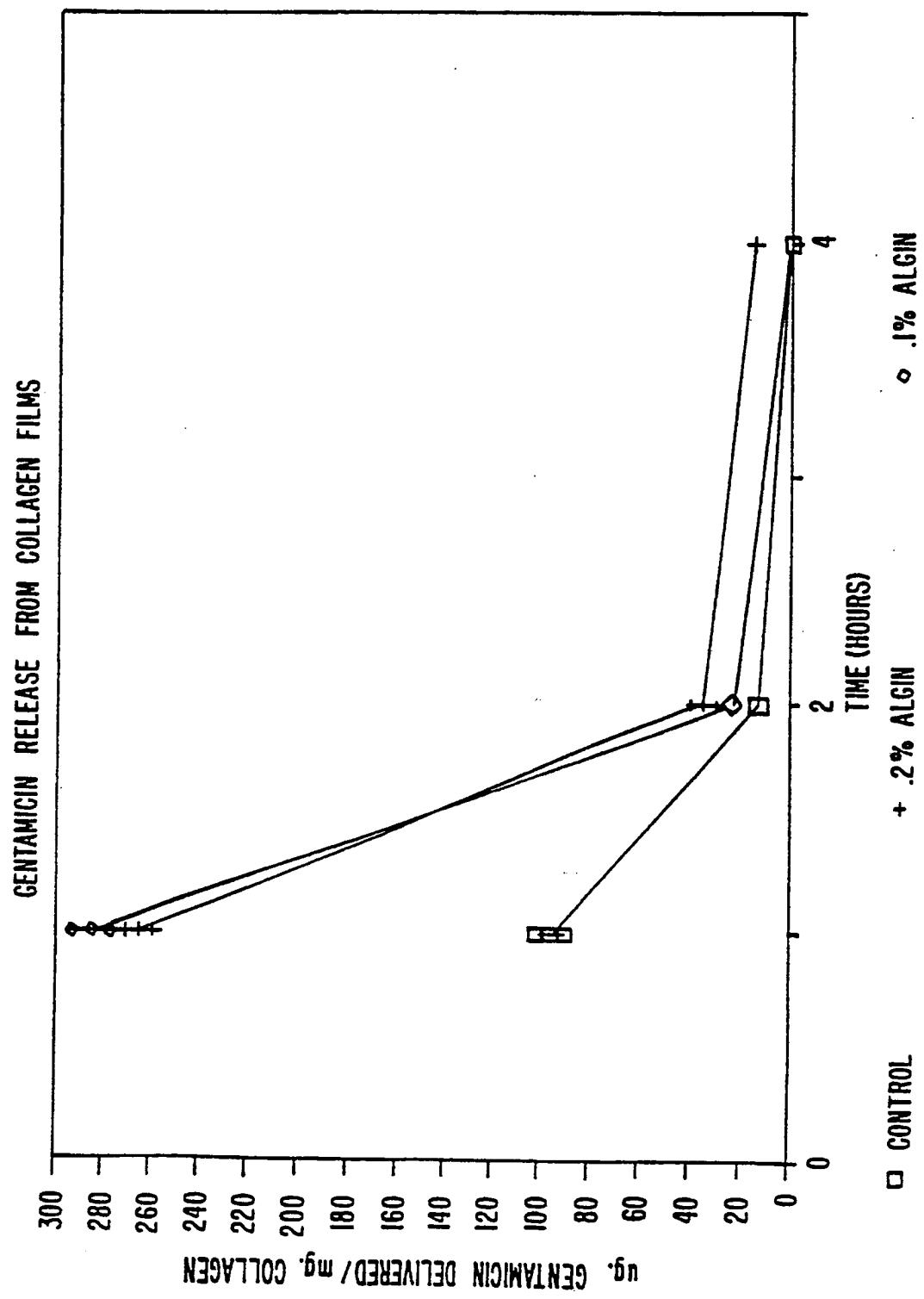


FIG. 2.

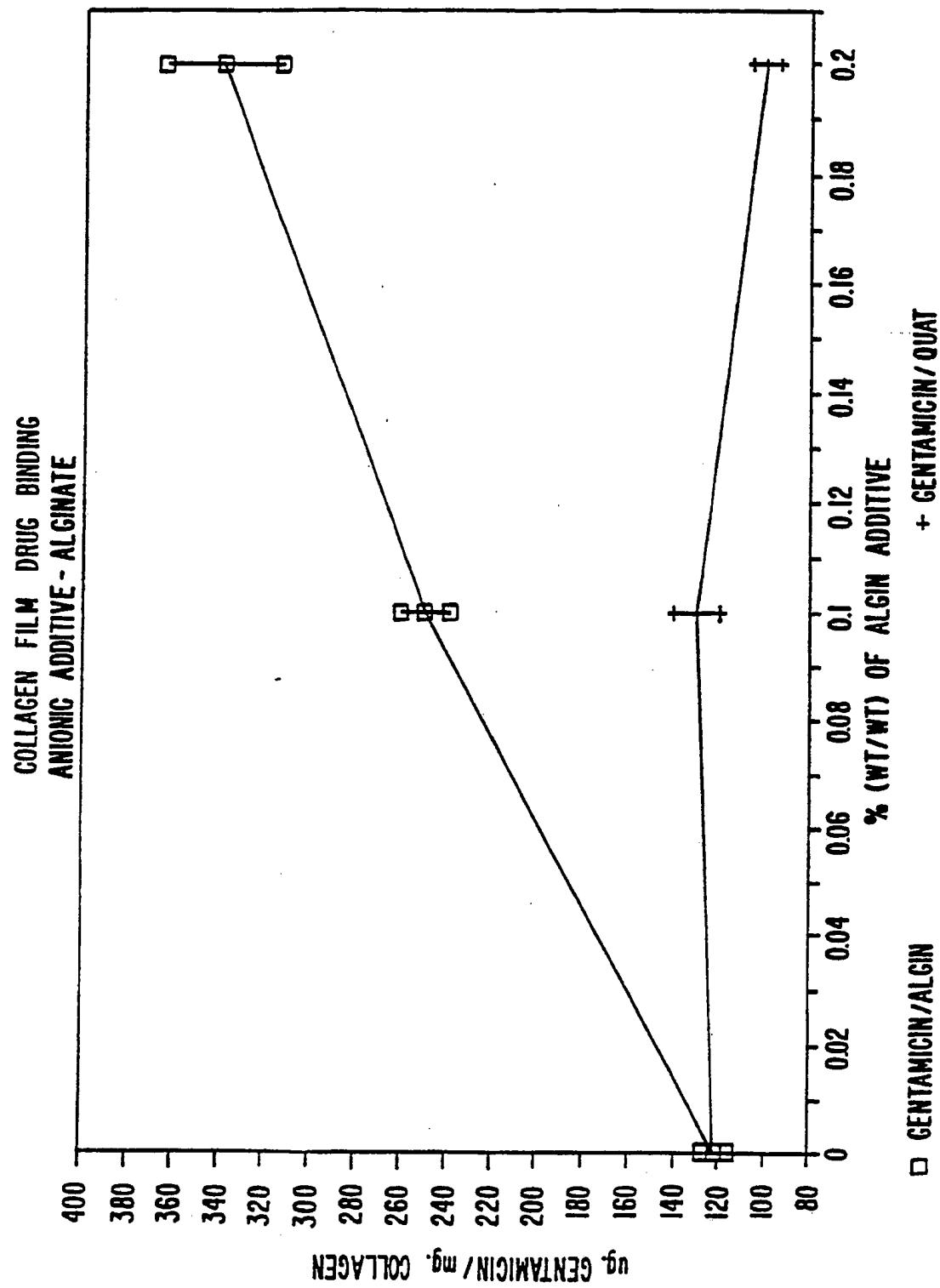


FIG. 3.

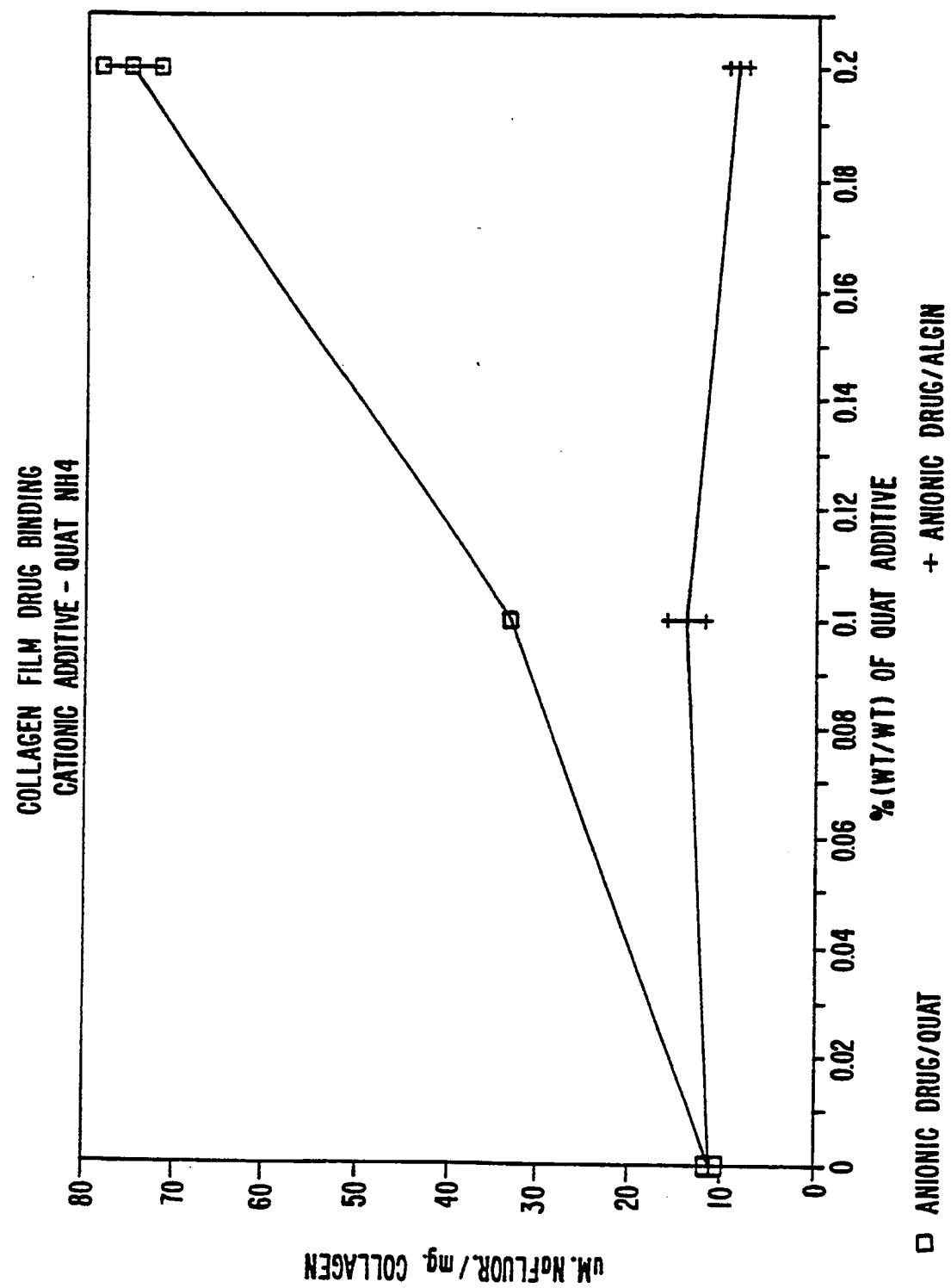


FIG. 4.

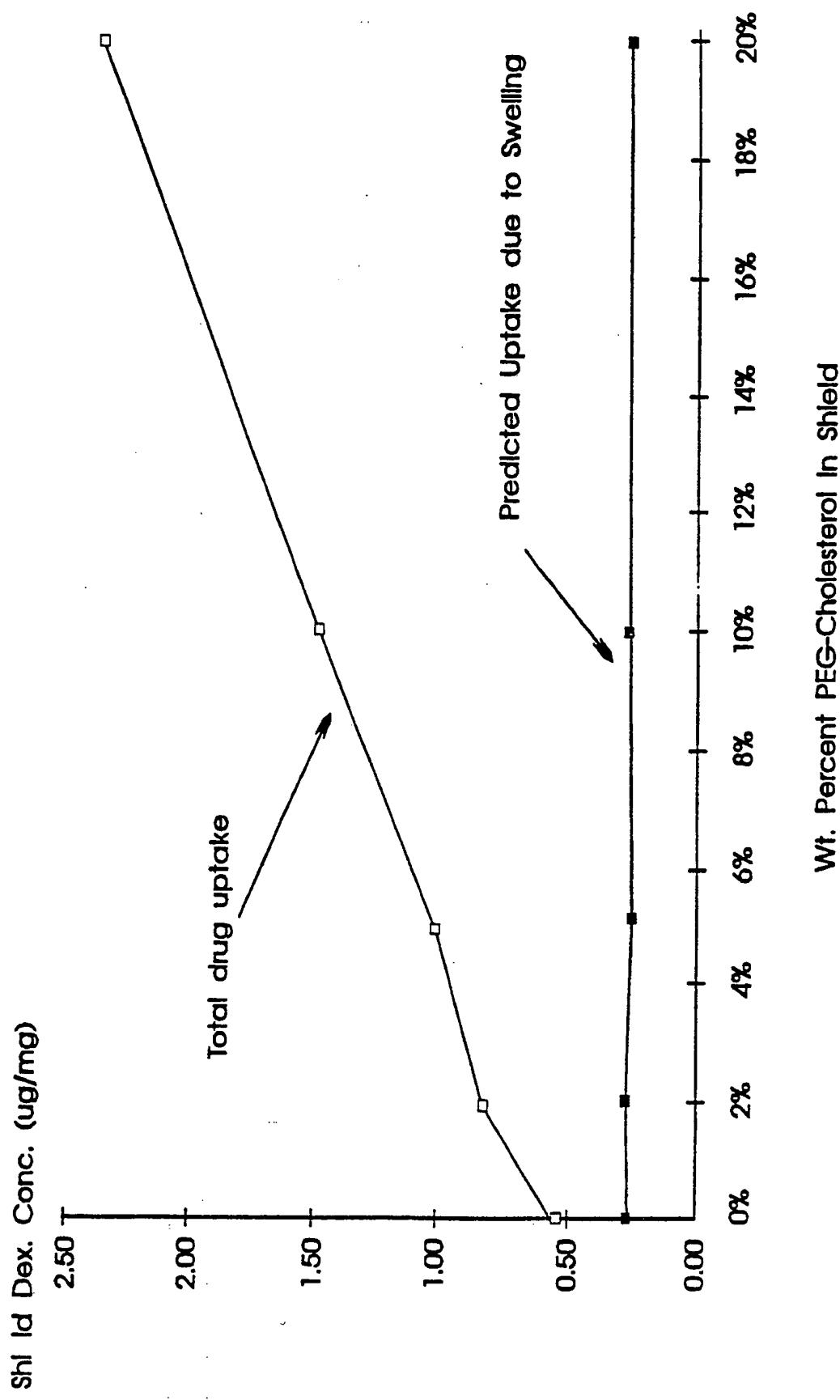


FIG. 5A

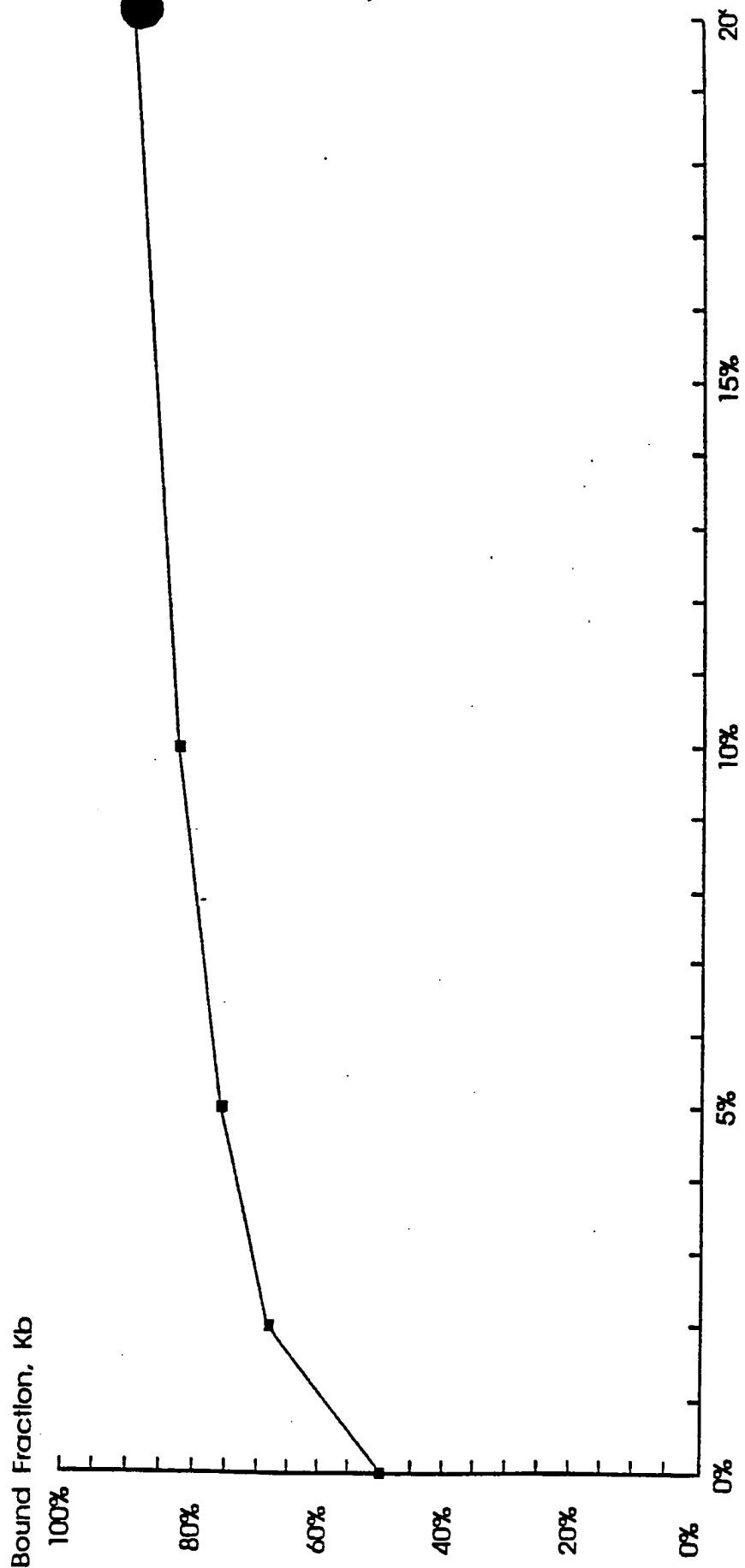


FIG 5B

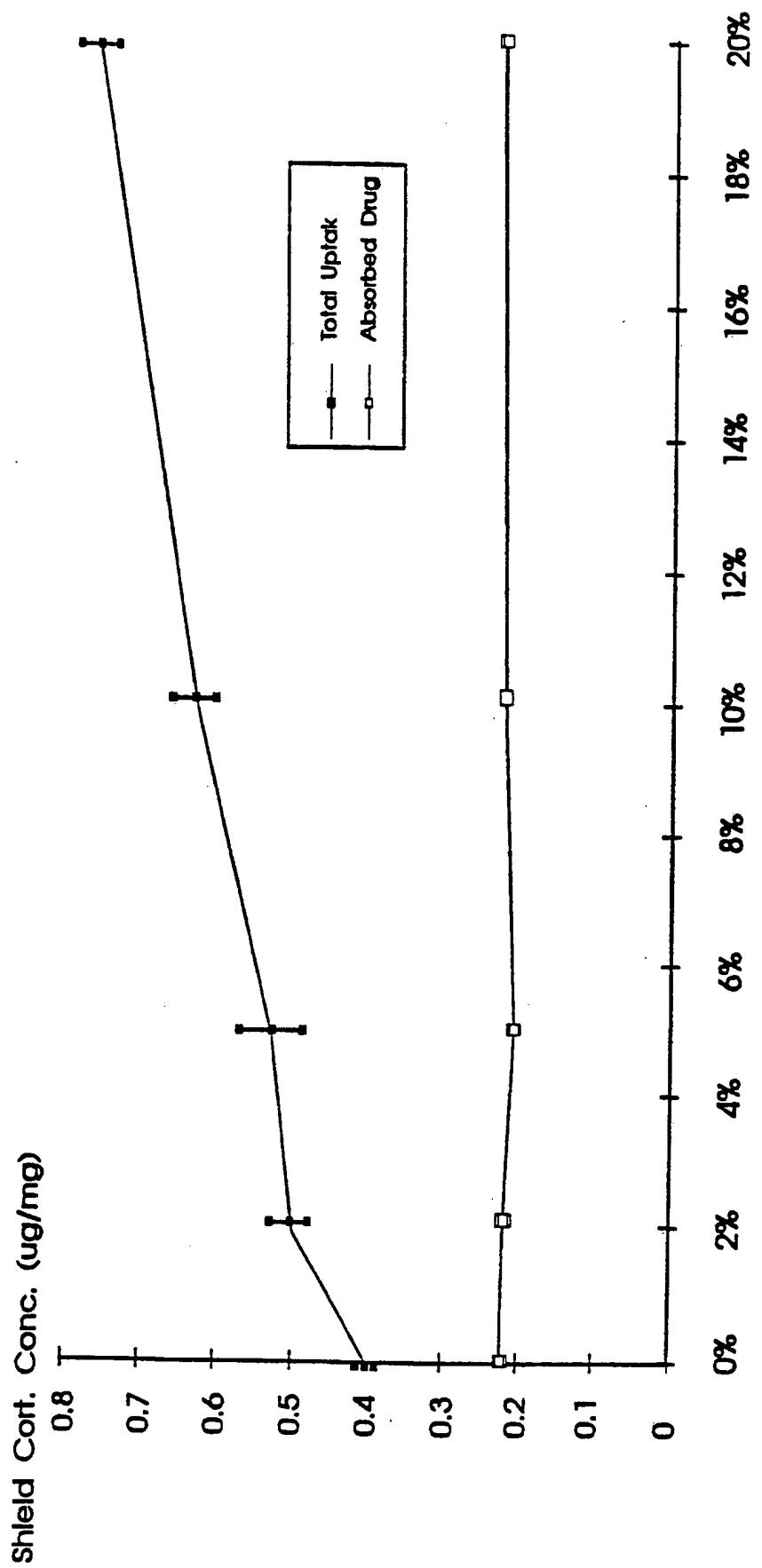


FIG. 6

Wt. Fraction PEG-Cholesterol In Shield

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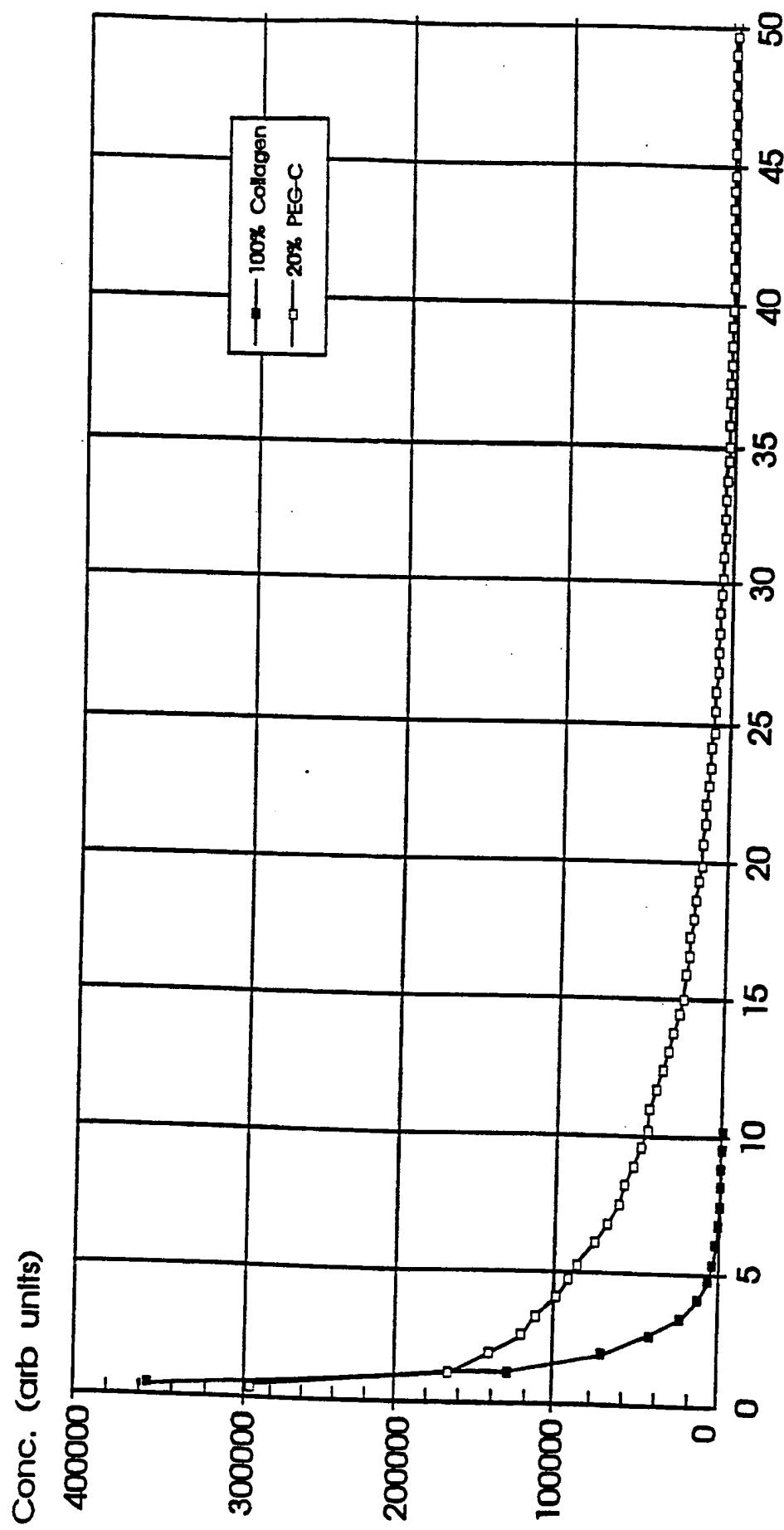
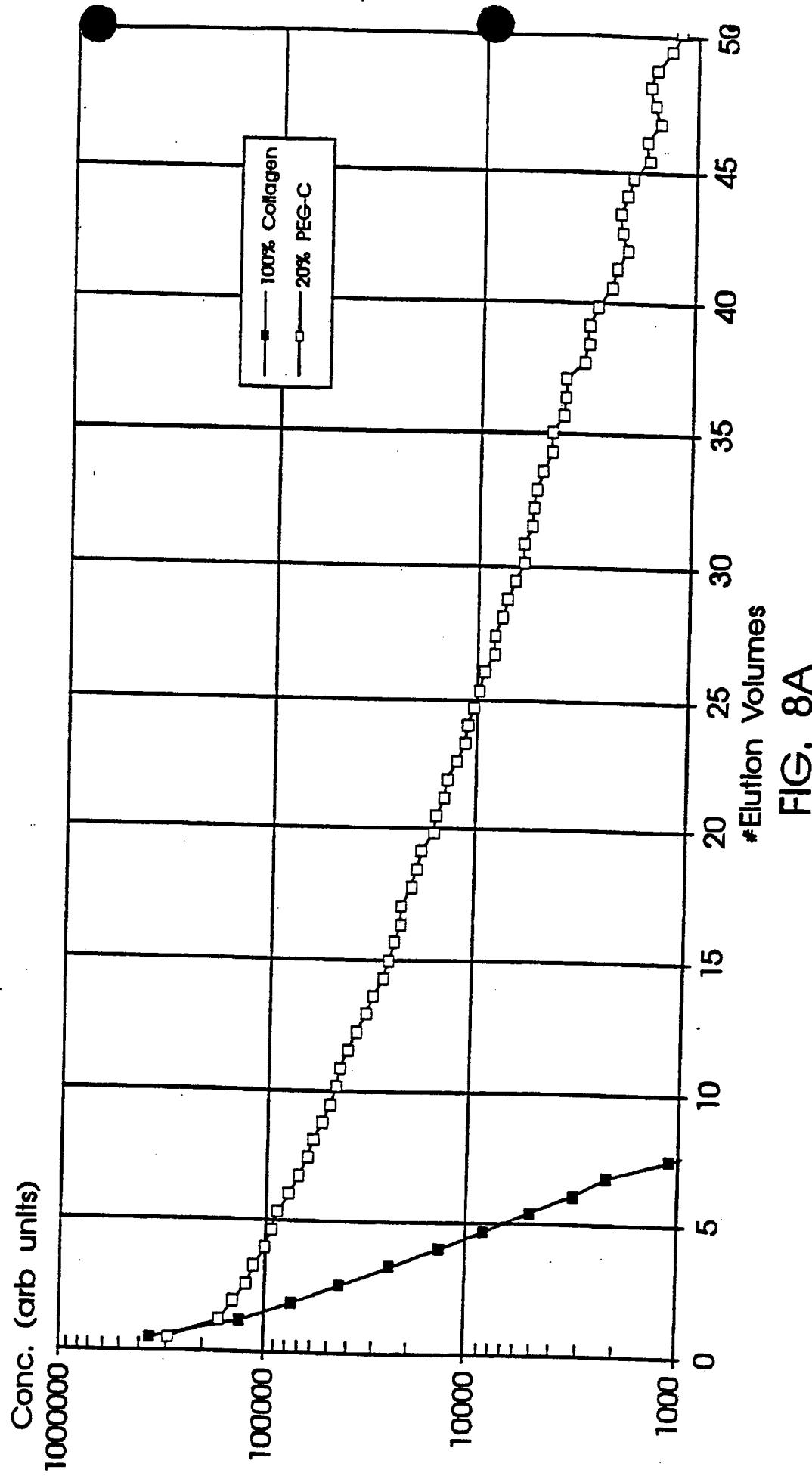


FIG. 7
Elution Volumes



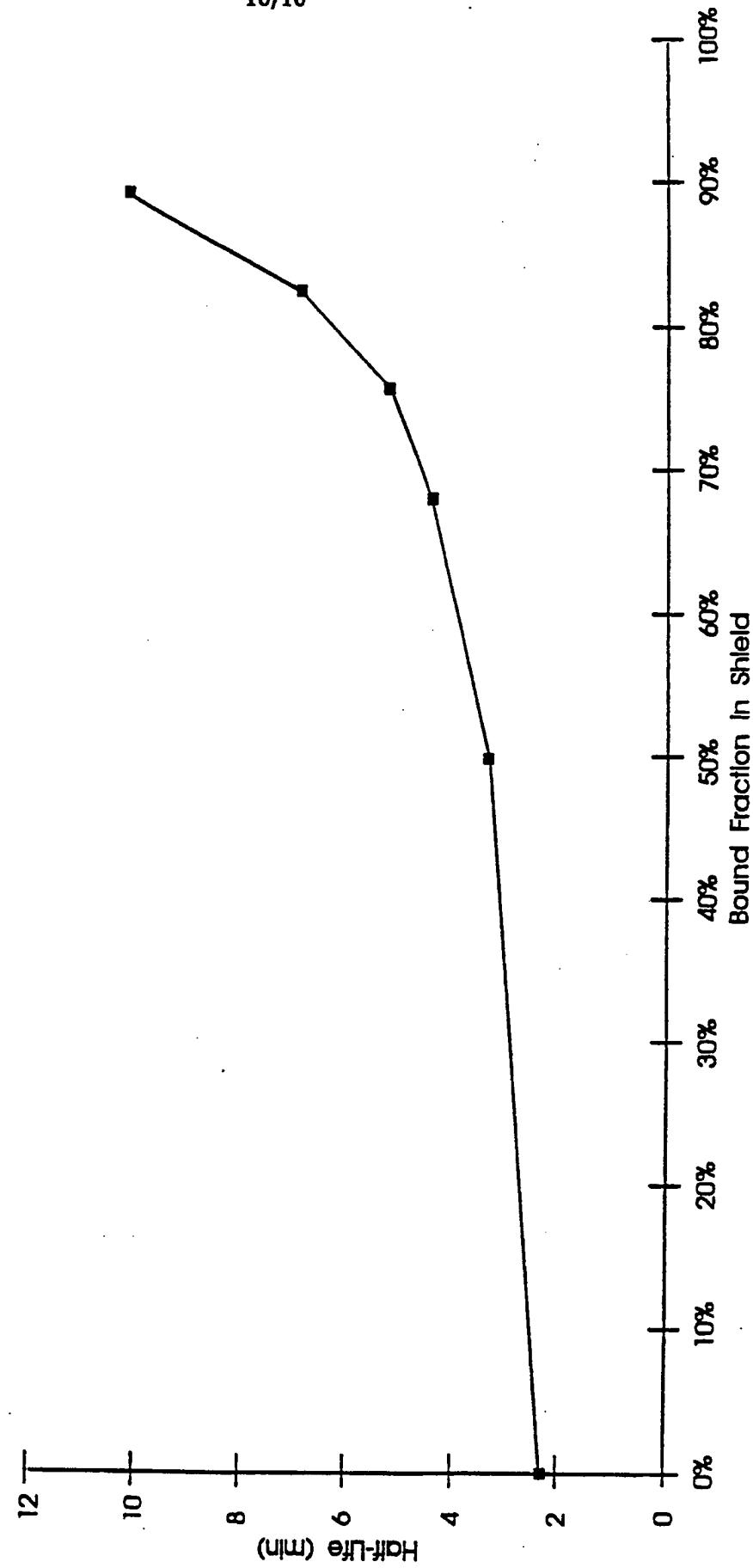


FIG. 8B

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/05606

A. CLASSIFICATION OF SUBJECT MATTER

IPC(S) : A61K 9/26

US CL : 424/427

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/427; 530/356

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 2,824,092 (THOMSON) 18 February 1958. See entire document.	1-25
Y		1-25
Y	US, A, 4,913,904 (POYODORV) 03 April 1990. See entire document.	1-25
Y	US, A, 4,865,846 (KAUFMAN) 12 September 1989. See entire document.	1-25
Y	US, A, 4,223,984 (MIYATA) 23 September 1980. See entire document.	1-25

Further documents are listed in the continuation of Box C. See patent family annex.

• Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be part of particular relevance		
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"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

24 AUGUST 1992

Date of mailing of the international search report

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Name and mailing address of the ISA/
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